REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

The prior claims have been canceled. New claims 31-45 have been added. New claim 31 corresponds to prior claim 28. Claims 32-45 are dependent from 31, and are similar to prior claims and find support in the claims now being canceled.

The instant invention now claimed is directed to treating leukemia in a human patient by administering via subcutaneous administration, a harringtonine salt, as defined in claim 31 or tautomeric form thereof, wherein the harringtonine is in a formulation in which:

(i) the pH of the formulation is between 5.5 and 8.5,

(ii) the harringtonines are in solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine, and

(iii) the level of chromatographic purity of harringtonine is higher than 99.7%.

Such a method is neither disclosed nor suggested by the prior art.

Claims 2, 4-6, 9, 10, 12-17, 19-21, 24-26 and 28-30 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Li et al or Takeda et al, together with Reg. No. H271 or Whaun et al. This rejection is respectfully traversed.

According to the Official Action, Li et al teaches injection of harringtonine and homoharringtonine in leukemia mice. Takeda et al is said to teach that "HA and HO had significant activates against P388 leukemia, L1210 leukemia ... by i.p. injection." Reg No. H 271 is said to teach subcutaneous administration of homoharringtonine. Whaun et

al is asserted to show subcutaneous injections at page 234, line 5. The Official Action concludes that, based upon the prior art, one skilled in the art would have been motivated to employ the known anti-leukemia drugs harringtonine and homoharringtonine by subcutaneous injection with a reasonable expectation that the drugs would be effective for treating leukemia. These same drugs were asserted to have been administered by subcutaneous injection for treatment of other conditions in Reg. No. H271 and Whaun et al.

The cited prior art fails to disclose or even suggest applicants' claimed invention. The harringtonine used according to the instant invention are specifically adapted formulations prepared from the salts forms, wherein the pH range of the formulation is between 5.5 and 8.5 *i.e.*, a neutral pH (*see, e.g.*, page 7, lines 9-14 of the specification). On the contrary, in all the cited references, the HHT being used is either the base form, or the salt form in a solution with a pH of less than 5.5.

The combination of cited references thus fails to disclose or even suggest the invention as claimed. The choice of this particular pH range leads to a compromise between the stability of the salt form of HHT (pK=3.5) and the tolerance of the product. As shown in Fig. 1 of the instant application, the formulation as recited in the instant claims has better bioavailability than the base form, as used in the cited art. Fig. 2 illustrates the good tolerance of this formulation, upon administration, as compared to the base form.

Such improved results upon subcutaneous administration of the base form at neutral pH is neither taught nor suggested by the prior art. The instant application thus shows unexpected results of the instant invention.

As previously argued, Li et al and Takeda et al only disclose that homoharringtonine (HHT) is effective when administered to leukemic mice. The instant claims are directed to human administration. These references thus fail to disclose or suggest the instantly claimed invention.

Nor does their combination with H271 and Whaun et al render obvious the claimed invention. First, there is no motivation to combine the cited references as proposed. There is no motivation for combining the primary references directed to administration in mice with the secondary references to obtain human, subcutaneous administration as instantly claimed.

One skilled in the art would have recognized that for a great number of anti-cancer compounds, subcutaneous mode of administration is dangerous. The reason is due to local toxicity, such as tissue necrosis. This is true, for example, for the antracyclin series, *i.e.*, toxorubicin, dororubicin and mitroxartrone, of anti-cancer compounds.

Moreover, the use of homoharringtonine by bolus intravenous injection causes cardiac problems, such as hypotension, because of the appearance of a homoharringtonine peak in blood. For this reason, continuous intravenous administration is preferred on human beings as compared to bolus or rapid intravenous injection. *See, for example,* Stewart et al, *Investigational New Drugs* 3:279-86 (1985), and Malamud et al, *AACR Abstracts*, p. 179, Abstract No. 709 (1984), enclosed herewith. Therefore, at the time of

applicants' invention, one skilled in the art would have believed that the subcutaneous route of administration would provoke the appearance of a homoharringtonine peak in blood, and thus also produce the same toxic effect on the heart as the bolus or rapid intravenous injection. This would have led one skilled in the art away from a subcutaneous route of administration.

Contrary to the rejection, H271 fails to show *in vivo* human results. Applicants note that H271 only states that the morphological modifications observed in tumoral cells in culture, then *in vitro*, are also observed *in vitro* in cultures of red cells. Although this reference further shows results concerning an *in vivo* test with subcutaneous administration of homoharringtonine, the results are in mice with malaria. These results neither disclose nor suggest that HHT could also be effective by the subcutaneous route in humans to treat leukemia. Leukemia is in no way related to malaria. One skilled in the art would not look to malaria treatments for treatments for leukemia.

The H271 reference reports clinical cancer studies showing safe dosages of 5 mg/m^2 of HHT administered by continuous infusion, *not* by subcutaneous route. This report only confirms the knowledge of the person skilled in the art, as summarized in the present application (*see, e.g.,* page 4), and does not suggest at all the subcutaneous treatment of leukemia in man by homoharringtonine.

This reference thus fails to overcome or remedy the deficiencies of Li et al and Takeda et al. The combination of Li et al and Takeda et al with H271 fails to render obvious the instantly claimed invention.

Applicants believe that Whaun et al also summarizes data obtained with cephalotaxine alkaloids drugs for the treatment of leukemia, but clearly states, "the method of administration was not reported...." *See*, page 231, line 1. Thus, Whaun also fails to overcome or remedy the deficiencies of the primary references. Whaun et al fails to teach or suggest the subcutaneous route for administration of HHT for treatment in humans with leukemia.

Whaun shows results of subcutaneous injections in *Plasmodium yoelii* infected mice. From this data, there would be no motivation for one skilled in the art to employ homoharringtonine by the subcutaneous route to treat leukemia in humans with reasonable expectation of effectiveness or success.

In view of the above data, the combination of references cited in the Official Action fails to disclose or even suggest the instantly claimed invention as claimed in claims 31-45. There is no teaching in the combined references of a method for treating leukemia in a human patient by administering via subcutaneous administration, a harringtonine salt, as defined in claim 31 or tautomeric form thereof, wherein the harringtonine is in a formulation in which:

(i) the pH of the formulation is between 5.5 and 8.5,

(ii) the harringtonines are in solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine, and

(iii) the level of chromatographic purity of harringtonine is higher than 99.7%.

Such a method is neither disclosed nor suggested by the prior art. As previously stated, prior to the instant invention, it was well known in the art that for a great number of

anti-cancer compounds subcutaneous mode of administration is dangerous due to local toxicity, such as tissue necrosis. This is true, for example, for the antracyclin series, *i.e.*, toxorubicin, dororubicin and mitroxartrone, of anti-cancer compounds.

Moreover, as previously stated, the use of homoharringtonine by bolus intravenous injection causes cardiac problems, such as hypotension, because of the appearance of a homoharringtonine peak in blood. It is for this reason that continuous intravenous administration is preferred on human beings as compared to bolus or rapid intravenous injection. *See, for example,* Stewart et al, *Investigational New Drugs* 3:279-86 (1985), and Malamud et al, *AACR Abstracts*, p. 179, Abstract No. 709 (1984), enclosed herewith. Therefore, at the time of applicants' invention, one skilled in the art would have believed that the subcutaneous route of administration would provoke the appearance of a homoharringtonine peak in blood, and thus also produce the same toxic effect on the heart as the bolus or rapid intravenous injection.

Surprisingly, applicants' invention shows that, although the administration causes the appearance of such a peak, it is not toxic and no cardiac problem or hypotension has been discovered in human beings resulting from the claimed method of treatment.

In addition, applicants' subcutaneous mode of administration has many advantages over the intravenous mode of administration. For example: (i) the patient can self inject the product; (ii) risks of septicaemia by the introduction of germs are null; (iii) overdoses are not possible, and (iv) subcutaneous mode of administration consists in discontinuous injection which permits the synchronization of the cellular cycle which is beneficial for the therapy (all the cells are in the same multiplication phase). This synchronization is

impossible, for example, when using continuous intravenous administration. The instant invention thus offers many advantageous and beneficial results, which were not expected prior to applicants' findings. *See also,* page 7, line 30 - page 8, line 30.

In view of the above, withdrawal of the rejection of record is respectfully requested. Such action is believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney at (650) 622-2360.

Respectfully submitted,

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